**Diabetic Retinopathy**

- Leading cause of death, disability and blindness in US for persons 20–74 yo
- Diabetes affects b/w 6.5 and 14 million Americans...50% may be undiagnosed
- Prevalence of DM
  - 10% for people ≥ 65 and
  - Rises to 16-20% for people ≥ 80 yo

**The Diabetic Patient**

What are the questions that you ask yourself when examining a diabetic?
The Diabetic Patient

- Look at the disc – specifically look for subtle NVD
- Are there hemorrhages or microaneurisms?
- Exudates, cotton wool spots?
- Look for the presence of NVE, traction, or VH
- Macular involvement?

What is the extent of the involvement?
That is the basis for classification

Diabetes Control and Complications Trial (DCCT)

- Multicenter, randomized trial involving over 1400 IDDM patients
- Intensive therapy reduced the risk of developing retinopathy by 76%
  - Slowed progression of retinopathy by 54% after a mean follow-up of 6.5 years
- Tight control reduced the cumulative 9-year incidence of CSME and PDR by 2-3 X
Hemoglobin HbA1

- HbA1C can tell you how high blood glucose has been on average over the last 8-12 weeks
- Normal non-diabetic HbA1C is 3.5-5.5%
  - In diabetes 4-6% is acceptable
  - > 7% is considered too high
- HbA1C test is currently one of the best ways to check if diabetes is under control

Diabetic Retinopathy

Pathologic process

- Microaneurysms
- Vascular permeability
- Ischemia
- Proliferation
- Cicatrization

Diabetic Retinopathy

Microaneurysms

- Earliest clinical sign
- Loss of pericytes
- Capillary closure
- Results: weakened wall -> biochemical and intraluminal pressure
- May be stable for years
Diabetic Retinopathy

Proliferation
- Stimulated by ischemia
- May be asymptomatic
- Within the vitreous
- Location and severity
Diabetic Retinopathy Classification

**Mild to Moderate Nonproliferative (NPDR)**
- Hemorrhages, microaneurysms
- Hard exudate
- Cotton wool spots (CWS)
- Minimal venous beading/IRMA
- Macular edema

**Severe Nonproliferative Diabetic Retinopathy**

**4-2-1 Rule**
- Hemorrhages & Macular edema in 4 quadrants *or*
- Significant venous beading in 2 quadrants *or*
- IRMA in 1 quadrant
Risk for Developing PDR in 1 yr

- Mild NPDR: 5%
- Moderate NPDR: 12%
- Severe NPDR: 52%
- Very Severe NPDR: 72%

Macular Edema

- Thickening of the retina
- Secondary to leaky microaneurysms
- 90% of visual loss in diabetes
- Increased progression following CE
- Watch for clinically significant macular edema (CSME)

Diabetic Retinopathy

Pathologic process

- Microaneurysms
- Vascular permeability
- Ischemia
- Proliferation
- Cicatrization
Diabetic Retinopathy

- Macular edema
  Defined as retinal thickening

Diabetic Retinopathy

- Clinically significant macular edema (CSME)
  Retinal thickening which involves or threatens the center of the macula

Early Treatment of Diabetic Retinopathy Study (ETDRS)

- To establish the effectiveness of argon laser tx and aspirin therapy in delaying or preventing the progression of early DR to advanced stages
- To determine the best time to initiate laser tx
- To monitor the effect of laser on visual function
- To produce natural history date, identify high risk groups
Early Treatment of Diabetic Retinopathy Study (ETDRS)

- 3711 patients in 22 centers
- Followed for 10 yrs
- 3 questions asked?
  1. Is laser Tx effective for macular edema?
  2. When in the course of retinopathy is Tx most effective?
  3. Does aspirin Tx alter progression of DR

ETDRS

- Began Dec 1979, completed July 1985
- Multi-center, randomized, clinical trial
- 3711 pts enrolled in 22 centers
- Follow up minimum of 4 yrs
- 1st reports published 1985

ETDRS Results

- Eyes with clinically significant macular edema (CSME) benefit significantly from argon laser photocoagulation
- Aspirin does not alter progression
- From ETDRS/DRS pts have a 95% chance of maintaining VA when guidelines are followed
ETDRS
Focal Laser
- Reduced the risk of moderate visual loss (MVA: VA < 20/200) by 50%
- Increased chance of visual improvement
- Decreased retinal thickening
- No major adverse effects

CSME
- Retinal thickening within 500 microns from the center of the FAZ
- Hard exudates associated with retinal thickening 500 microns from center of FAZ
- Zones of retinal thickening > 1 DD in area, any part of which is 1 DD from the center of the fovea

CSME
- Visual acuity is not part of the definition
- VA ranged from 20/10 to 20/200 at entry into the ETDRS
CSME

- Involves the center of the fovea
- Threaten the center of the fovea
  - Small but near the center
  - Away but large

Patterns of CSME

- Focal
- Multifocal
- Circinate ring of exudate
  - Leakage in center of the ring
- Diffuse leakage

Diabetic Macular Edema

Diagnosis

- FA leakage without thickening is **not** CSME
- 60D, 78D, 90D lens are **not** as good as CL
Treatment of DME

- Angiogram and VA are not used to define CSME
- Tx benefit in CSME is most marked with center involved and moderate VA loss
- Most DME treated with focal (some grid)

Diabetic Macular Edema

- Focal laser: directly to leaky microaneurysms
- Scatter (grid): diffuse pattern of Tx
- Macular capillary nonperfusion may not benefit from laser Tx

Patterns of Leakage in DME

- Poor prognosis
  - Chronic leakage
  - Lipid deposits
  - Capillary nonperfusion
  - Perifoveal capillary dropout
ETDRS Results

Tx proven to be effective:
- Regardless of baseline VA
- Moderate NPDR + ME
- Subjective improvement

Re-Treatment of DME
- 4 month intervals if CSME and treatable
- Sooner, only if missed original treatment

Intravitreal Steroid Injection
- 1st used in early 1980’s for refractory CME following CE, mostly periocular
- Gaining popularity in Tx of retinal neovascularization, CNV, PVR
- Several recent papers advocating intravitreal steroid injections for refractory DME
Intravitreal Triamcinolone for Refractory DME
Martidis A, Duker JS, Greenberg PB et al.
Ophthalmology May 2002; 109:920-927

- Tx 16 Eyes CSME, at least 2 prior lasers Tx
- 4 mg Triamcinolone acetonide
- Mean ↑ VA 2.4 lines @ 1 and 3 mo,
  - 1.3 lines @ 6 mo
- OCT thickness ↓ 55% @ 1 mo; 57.5% @ 3 mo; 38% @ 6 mo
- 8 of 16 completed 6 mo follow up

IOP Spikes Following Intravitreal Steroid Injection

- IOP > 21 develops in ~ 50% of eyes
  - IOP spike > 10 occurs in 30%
- 1-2 months following injection
- Returns to normal after 6 mo
- Most normalized with topical IOP meds

Optometric Management of Diabetic Patient

- No diabetic retinopathy
  - Educate and follow yearly
- Early or moderate NPDR
  - Establish presence of CSME
    - If CSME refer to retina specialist
  - No CSME
    - Educate
    - Follow yearly
Optometric Management of Diabetic Patient

- Severe NPDR
  - Follow every 4 months
- PDR: refer to retina specialist

Proliferative Retinopathy (PDR)

- Vitreous hemorrhage
- NVD
- NVE
- Fibrovascular proliferation
- Retinal detachment

Important Historical Significance!

- Is light photocoagulation safe and effective in treating diabetic retinopathy?
  - 1972 NEI launched the DRS
  - 1st large collaborative controlled clinical trial in the history of ophthalmology!
  - By 4 yrs the study provided valid clinic data to provide a scientific basis for photocoagulation
**Diabetic Retinopathy Study (DRS)**

- Began 1972, stopped after 4 yrs
- Provided scientific basis for photocoagulation
- PRP demonstrated an overall reduction in rate of severe VA loss (< 5/200) from 15.9% to 6.4% in Tx eyes
- Reduced the risk of severe VA loss by 60%
- Established high risk groups in PDR

**PDR**

**High-Risk PDR**

- NVD > ¼-1/3 disc areas
- NVD with preretinal or VH
- NVE > ½ disc areas with preret heme

- Severe visual loss develops in 25-40% within 2 years

**The Role of VEGF in DR**

- VEGF – Vascular endothelial growth factor
- Best-described as mediator of ocular angiogenesis
- Important mediator of development of neovascularization
  - AMD
  - Retinal vascular disease
**VEGF and Diabetes**

- Increases vascular permeability through specific binding to receptors on vascular endothelial cells
- Affects selective endothelial cell mitogenic activity and regulation by hypoxia
- NIH study recruiting pts
  - EYE001 (anti-VEGF pegylated aptamer)

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**Age-related Macular Degeneration (AMD)**

- Degenerative disorder that affects the macula
- Leading cause of legal blindness in people > 65 yo
- 90% of vision loss is 2° to CNV
  - Develops in 1.2% of adults 43-86 yo (Wisconsin Beaver Dam Eye Study)

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**ARMD**

- Patients Affected
  - 10% wet or exudative
  - 90% dry or nonexudative
- VA < 20/200
  - 80-90% exudative
  - 10-20% dry
AMD Pathophysiology

Not clearly understood
- Genetic compromise of RPE that affected by the environment
- Photostress
- Dietary deficiency of antioxidants
- Cardiovascular risk factors

Dry ARMD

- Earliest clinically detectable feature
- Lie between BM of RPE and Bruch's
- Hard drusen: smaller, calcified or ossified
- Soft drusen: ill-defined, larger, coalesce, resemble small serous detachments

Exudative/Wet ARMD

Fluid leakage
- Degenerated Bruch’s membrane
- Loss of RPE adhesion
- New vessel growth (CNVM)
Type I Vs Type II CNV

Clinical Sign of CNV
- Subretinal fluid
- Subretinal hemorrhage
- Exudate
- Gray-green pattern of pigment
Growth of CNV
- Growth simulates seafan or bicycle tire spokes
- Early, blood flow is slow: no fluid, exudate
- Exudation/leakage as membranes matures
- FA: early fluorescence which builds in intensity
- Active leakage late phase - > loss of definition

Classification CNV
- Classic - well defined on FA
- Occult – represent 70% of CNV
  - Poorly defined by FA – nondistinct borders
  - Stippled hyperfluorescence, with late leakage
- Mixed

Classic Choroidal Neovascularization
- VA = 20/300
- Inferior Superior
Classification CNV

Occult CNV
- Predominantly Classic
  - Area of classic CNV ≥ 50% of the lesion
- Minimally Classic
  - Area of classic component < 50% of the lesion
- Occult-only
  - No classic component

Classification CNV

Choroidal Neovascular Membranes (CNV)
- Invade Bruch’s membrane
- Perforate intact Bruch’s membrane
- Grow through defects in Bruch’s
**CNV**

- Significant cause of vision loss in both the working class and geriatric population
- Mechanism is not completely understood
  - Any pathologic process that involves RPE and damages Bruch’s membrane can be complicated by CNV
  - What is the stimulus that causes the growth of CNV?

**Treatments for CNV**

- Where have we been?
- Where are now?
- Where are we going?

**Where have we been?**
AMD: Established Therapies

◆ Thermal laser photocoagulation
◆ Photodynamic therapy with Visudyne™
  ◆ FDA approved for:
    ▶ Subfoveal predominantly classic lesions
    ▶ Subfoveal minimally Classic or Occult-only – but Lesions must be < 4DD in size – or must be demonstrated disease progression
◆ Anti-VEGF Therapy

Photodynamic Therapy (PDT)

◆ Photosensitizing dye (Verteporfin)
◆ Slow infusion into the arm
◆ Drug activated by nonthermal laser light – 689 nm
◆ Photochemical reaction results
◆ Leads to platelet activation -> thrombosis and occlusion of CNV

The ABC’s of PDT

◆ TAP:
  ◆ Treatment of AMD with Photodynamic Therapy
◆ VIP:
  ◆ Verteporfin in Photodynamic Therapy
◆ VIP-PM:
  ◆ Pathologic Myopia
◆ VOHS:
  ◆ Verteporfin in Ocular Histoplasmosis
◆ VIM:
  ◆ Vertiporfin in Minimally Classic CNV
◆ VER:
  ◆ Early PDT Retreatment
◆ VALIO:
  ◆ Altered Light in Occult CNV
**PDT Outcomes**

- Benefit at 1 and 2 yrs with subfoveal Classic CNV
- No benefit with Minimally-classic CNV
  - Classic component < 50% of CNV
- Occult-only CNV: benefit at 2 yrs (no benefit seen at 1 yr)
  - Subgroup analysis showed smaller lesions (< 4 DD) and VA 20/50 or worse had the greatest treatment benefit

**How Effective is PDT?**

- From the TAP study, successfully treated patients averaged 20/160-2 at 24 months
- Patients often need multiple treatments.
  - 5.6 treatments (TAP study) and 4.9 treatments (VIP study) over 24 months

**With Treatment, Average Outcome is a Loss of Vision...**

<table>
<thead>
<tr>
<th>Follow-up visit (months)</th>
<th>Mean visual acuity loss (letters)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>-30</td>
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<tr>
<td>3</td>
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</tr>
<tr>
<td>18</td>
<td>5</td>
</tr>
<tr>
<td>21</td>
<td>10</td>
</tr>
<tr>
<td>24</td>
<td>15</td>
</tr>
</tbody>
</table>

- Predominantly classic treated (n=159)
- Occult-no classic* treated (n=123)

*VA ≤20/50 or lesion size ≤4 MPS DA

TAP Study Group 2001; VIP Study Group 2001
Follow-up visit (months)

Predominantly classic placebo (n=83)
Occult no classic* placebo (n=64)

Mean visual acuity loss (letters)

*VA ≤ 20/50* or lesion size ≤ 4 MPS DA

TAP Study Group 2001; VIP Study Group 2001

Where are we now?

Does this represent the future?

Vascular Endothelial Growth Factor (VEGF)

- Multifunctional protein
- Mediator of developmental and pathological vascularization
- Angiogenic and vascular permeability properties
VEGF – Common Denominator in AMD

Predominantly Classic

Occult with no Classic

Microvascular Research 2002;64:162-169

VEGF-A Is a Member of a Family of Angiogenic Growth Factors

◆ 5 Different isoforms of VEGF with varying numbers of amino acids and mRNA
  - VEGF206
  - VEGF189
  - VEGF165
  - VEGF145
  - VEGF121

◆ Homodimeric glycoprotein
◆ Secreted by a variety of cells

VEGF

◆ VEGF165 is selectively increased during pathological neovascularization
◆ Blocking VEGF165 inhibits pathological neovascularization; spares normal vessels
**Anti-VEGF Therapy**

- Represents 1st validated biologic switch in the treatment of pathologic CNV
- Major paradigm shift in how we treat neovascular and hyperpermeability diseases
- Targeting the root cause of CNV

**FDA Approved Dec 17, 2004**

N Eng J Med: Dec 31, 2004

**Macugen (Eyetech/Pfizer)**

- Synthetic fragment of a genetic material referred to as an aptamer
  - Aptamers are nucleic acid ligands that are isolated from oligonucleotides
- Binds to the VEGF165 molecule and blocks it from stimulating the receptor on the surface of the endothelial cell
**V.I.S.I.O.N. Study Design**
- Two randomized, double-masked, sham-controlled, dose-ranging trials involving 1053 patients

<table>
<thead>
<tr>
<th>Macugen 0.3 mg</th>
<th>Macugen 1 mg</th>
<th>Macugen 3 mg</th>
<th>Usual Care</th>
</tr>
</thead>
</table>

Source: Eyetech Pharmaceuticals, Inc.
- Treatment regimen: Every 6 weeks
- Pre-specified time point for primary endpoint - 54 Weeks
- PDT was permitted per FDA-approved label at the masked investigator’s discretion

**Pegaptanib Sodium: Safety**
- 1,053 patients by 117 centers worldwide
- 7,545 intravitreous injections performed in No evidence of systemic side effects
  - No evidence of ocular drug-related side effects
  - Ocular adverse events related to the route of administration were seen
    - Majority were mild and transient
    - Serious AEs were infrequent and manageable
- Conclusion: A favorable safety profile

**V.I.S.I.O.N. Phase 3 Data**

![Graph showing VAS Change (mm) over weeks for Year One and Year Two for 2 Years' Treatment (N=133) compared to Usual Care (N=107). The graph indicates a 45% benefit at P<0.01.](image)
Lucentis (Genentech)

- Recombinant humanized antibody “fragment” binds to VEGF
- Targets a different isoform of VEGF than Macugen
- Prevents VEGF from interacting with the VEGF receptor on the surface of endothelial cell
- Injected into vitreous
- Transparent jelly-like substance fills the vitreous cavity
  - Rapidly passes through the retina and into the subretinal space to the RPE (1hr)

Ranibizumab for Neovascular Age-Related Macular Degeneration

Philip J. Rosenfeld, M.D., Ph.D., et al., for the MARINA Study Group

Lucentis Phase III Clinical Trials

- MARINA trial
  - AMD pts with subfoveal minimally classic or occult-only CNV tx with monthly injections 300g or 500g vs. sham
  - Followed for 24 months
- ANCHOR trial
  - Predominantly classic CNV to receive monthly injections of 300g or 500g vs. PDT
  - Evaluated q 3 mo then receive PDT vs. placebo
  - 1st endpoint is loss of at least 15 letters of VA
Principal Eligibility Criteria

- Age ≥50 years
- VA (Snellen equivalent) 20/40 to 20/320
- Subfoveal CNV secondary to AMD
- No prior PDT
- Lesion composition by fluorescein angiography
  - Area of CNV must be ≥50% of total lesion
  - Minimally classic or occult with no classic
- Evidence of presumed recent disease progression
  - Blood, recent growth by FA, or recent VA loss
- Lesion size ≤12 disc areas (DA)

Trial Design: Phase III, Randomized, Multicenter, Double-Masked, Sham-Controlled Study

Investigator identifies potential subjects

Reading center confirms angiographic eligibility

Minimally classic or occult with no classic lesions (N=716)

Randomization 1:1:1

Sham (n=238) Ranibizumab 0.3 mg (n=238) Ranibizumab 0.5 mg (n=240)

Secondary Endpoint:
Mean Change in Visual Acuity Over Time

Sham (n=238) Ranibizumab 0.3 mg (n=238) Ranibizumab 0.5 mg (n=240)

Note: Vertical bars are ± one standard error of the mean.

*P<0.0001
**Letter Gains From Baseline**

![Graph showing letter gains from baseline for Ranibizumab 0.3 mg (n=238), Ranibizumab 0.5 mg (n=240), Sham (n=238) at Month 12 and Month 24.](image1)

*Pre-specified secondary endpoint
†P<0.0001; ‡P=0.008; §P=0.002; **P=0.0015; ††P=0.0007 vs sham.

**Exploratory Endpoint:**

**VA 20/40 or Better**

![Graph showing percentage of subjects achieving VA 20/40 or better for Ranibizumab 0.3 mg (n=238), Ranibizumab 0.5 mg (n=240), Sham (n=238) at Baseline, Month 12, and Month 24.](image2)

*P<0.0001 vs sham.

**Conclusions: 2-Year Results**

- Ranibizumab demonstrated a clinically and statistically significant benefit over sham through 24 months of treatment
  - ≥90% of subjects lost <15 letters
  - 5.4- to 6.6-letter improvement in mean VA compared to baseline
  - ~20-letter benefit compared to sham
  - 26% to 33% improved ≥15 letters
  - 5% to 5.8% improved ≥30 letters
  - Other visual and anatomical outcomes favored ranibizumab
A Phase III Study of Ranibizumab (LUCENTIS) for Intravitreal Injection vs Verteporfin (Visudyne®) PDT in Predominantly Classic Subfoveal Neovascular AMD — Year 1 Results —

Principal Eligibility Criteria
- Age ≥ 50 years
- VA (Snellen equivalent) 20/40 to 20/320
- Primary or recurrent subfoveal CNV lesion secondary to AMD
- No prior PDT
- Lesion composition by fluorescein angiography
  - Classic CNV ≥ 50% of the total lesion area (predominantly classic lesion)
  - Total lesion ≤ 5400 μm in greatest linear dimension

Trial Design: Phase III, Randomized, Multicenter, Double-Masked, Active Treatment-Controlled Study
- Investigator identifies potential subjects
- Reading center confirms angiographic eligibility
- Predominantly classic lesions (N=423)
- Randomization 1:1:1
- Verteporfin
- Sham PDT
- Sham injection (n=143)
- Ranibizumab 0.3 mg (n=140)
- Ranibizumab 0.5 mg (n=140)
Secondary Endpoint: Mean Change in Visual Acuity Over Time

- PDT (n=143)
- Ranibizumab 0.3 mg (n=140)
- Ranibizumab 0.5 mg (n=139)

Note: Vertical bars are ± one standard error of the mean.

Letter Gains From Baseline at Month 12

- Gain in VA (ETDRS letters)
- PDT (n=143)
- Ranibizumab 0.3 mg (n=140)
- Ranibizumab 0.5 mg (n=139)

Exploratory Endpoint: VA 20/40 or Better at Month 12

- PDT (n=143)
- Ranibizumab 0.3 mg (n=140)
- Ranibizumab 0.5 mg (n=139)

*Pre-specified secondary endpoint
Conclusions

- Ranibizumab treatment resulted in a clinically and statistically significant benefit compared to PDT in predominantly classic CNV after 12 months of treatment
  - ~95% of subjects lost fewer than 15 letters
  - 8.5- to 11.3-letter improvement in mean VA compared to baseline
  - 36%-40% gained ≥15 letters
  - 6%-12% gained ≥30 letters
  - Other visual and anatomic outcomes favored ranibizumab

Lucentis Phase III Results: MARINA and ANCHOR Trial

- 95% treated eyes maintained vs. 60% control group at 12 and 24 months
- 40% of treated patient had 20/40 VA vs. improvement in VA
- 90% treated with Lucentis at year two maintained or improved vision compared to 53% in the control arm

Conclusions

- Ocular serious adverse events occurred in <0.1% of intravitreal injections
- No imbalance in nonocular adverse events overall
Lucentis™

Lucentis (ranibizumab-rhuFabV2) is the first treatment that results in improvement in visual acuity.

Avastin® (bevacizumab, Genentech Inc.)
First anti-VEGF therapy approved by the FDA

FDA approved as a first line therapy for metastatic colorectal cancer on February 26, 2004

Lucentis™ (rhuFab V2, ranibizumab) is derived from Avastin® (bevacizumab)

Avastin-Fab
MW 48 kD

Avastin® Bevacizumab
MW 150 kD

Lucentis™ Ranibizumab
MW 48 kD
140X higher affinity for VEGF
Lucentis (Ranibizumab) has a higher affinity for VEGF

\[ K_d \approx 1.0 \text{ nM} \quad \text{versus} \quad K_d \approx 0.14 \text{ nM} \]

*based on values in published reports

Why consider Avastin in ophthalmology?

- Patients losing vision on current therapies
- Lucentis and Avastin have nearly identical binding properties
  - Functionally the same molecule
- Avastin is available off-label
- Intravitreal Lucentis improves vision but not yet FDA approved

Intravitreal Avastin for Neovascular AMD

- First patient treated in May, 2005
- Case reports published in July, 2005
- Global clinical use in less than 6 months
- Medicare coverage in a majority of states
Lucentis vs. Avastin (Genentech vs Genentech)

COST
- Lucentis -> $2500 - $3,000 per injection
  - $3300 per mg
- Avastin -> $5.50
  - 1.25 mg costs $6.88
- If dispensed by a licensed pharmacist directly from the vial to the syringe, cost rises to between $17 and $50 a syringe

Summary
- Anti-Angiogenic therapy appear to be the future for the treatment of CNV and retinal vascular disease
  - Represent a major shift in the paradigm of Tx for CNV
  - Lucentis and Avastin have shown remarkable results beyond what has been seen previously